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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,158	02/17/2004	Juan C. Colberg	PC10856B	6044

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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,158	COLBERG ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-12,32,34 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8-12,32,34 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/20/05 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-6, 8-12, 40 are rejected under 35 U.S.C. 112, paragraphs 1 and 2, as the claimed invention is not described, or is not described in such full, clear, and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Specifically:

The claim 1 process, as written, will not produce the product as specified, and hence the claim is not correct (paragraph 2). Alternatively, the specification does not teach how to do this process (paragraph 1). The problem here is the XH in the final product of Formula 1. Example 1 exactly corresponds to the claim 1 process language, including the PCl_5

treatment at page 27, lines 26-27. The product, however, does not correspond to Formula 1 because the HX is not present. No other example gives the Formula 1 product either. The Bateson et al. reference, doing the N-deacylation on a virtually identical compound (differing only in the nature of the ester group at a remote point) does not directly obtain the salt. Either the structure of Formula 1 is not correct, or something has been left out. If the examples fail to produce the product, the claims are not enabled, *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190.

In responding to the rejection, applicants must first decide for themselves whether or not they believe that claim 1 is correctly written, i.e. whether they intend that claim 1 be a process giving a process with HX present. If applicants decide that the claim is not correctly written, they must amend the claim, being careful not to introduce new matter. If applicants decide that the claim is correctly written, applicants must explain the discrepancy between the process as set forth in the claim, with HX present, and the process as set forth in example 1 of the specification and also in Bateson, with HX not present. That is, since the specification teaches that this process gives a process with HX not present, a process with HX present cannot be deemed enabled. When operativeness has been properly challenged, it is incumbent on applicant to limit the claims accordingly, cf. *In re Harwood*, 156 USPQ 673, *In re Cook*, 169 USPQ 298, I*n re Langer*, 183 USPQ 288, *In re Corkill*, 226 USPQ 1005, 1009, and *In re Rainier*, 153 USPQ 802. The fact that the specification itself teaches that this process gives a product with HX not present presents a proper challenge to the operativeness of the claims.

The traverse is unpersuasive. The response completely fails to address the fact that the actual working example 1 failed to give the product. The remarks state, "When the

process of claim 1 is followed, the product is a compound of Formula I, which is the hydrochloride salt." However, example 1 in the specification does follow claim 1, including the use of PX_5 which applicants state "provides the X for the XH portion", and the product is NOT Formula I. The remarks do not address this discrepancy at all, and in fact make no mention at all of example 1.

With regard to Bateson, the arguments are unpersuasive. The declaration is noted, and the remarks talk about purity and yield. However, that is not relevant to this rejection. The point is that Bateson is a second piece of evidence that the use of PX_5 does not give the HX salt.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 8-12, 32, 34, are rejected under 35 U.S.C. 103(a) as being unpatentable over Bateson et al (US-6,001,997).

The claim 1 process is embraced by the teaching of the reference at column 11, line 41-column 12, line 19. Converting the product to a salt appears as step v) at line 65, making the salts referred to at column 2, line 20. The p-nitrobenzyl choice for R3 (for claim 28) appears at column 3, line 17, and allyl (for claim 29) is at line 18 and benzyl (for claim 30) is at line 16. The actual examples use the p-methoxybenzyl ester (e.g. 6, 13-15) or the butyl (example 1). The equivalence of the groups is clearly taught at column 3, lines 16-18,

where all 5 groups are mentioned. Applicants need to show that unexpected effects arise from the use of one protecting group rather than another. Similarly, the p-methoxybenzyl and butyl esters of the 7-amino compounds of examples 1, 3, 6, 13-15 render claim 32 obvious. These fall within Formula II, differing only in the carboxyl protecting group, which is obvious for reasons set forth above, and being in the salt form, a variation taught by column 9, line 29. In the same manner, the phenylacetamido intermediate of claim 33 is rendered obvious by the intermediates at example 6, step d; example 13, step e; examples 14-15, step d. This differs solely in the nature of the carboxyl protecting group.

Claim 2's toluene is seen in e.g. example 1, step e; example 3, etc. Claim 3's use of PCl_5 is seen in e.g. example 1, step f; example 15, step e, etc.

The preliminary steps (formerly in claims 4 and 7) which deal with the process of preparing the starting material IIIa, converting the alcohol IIIc to the halide IIIb, and reacting that with the phosphine appear in the reference at column 12, lines 22-48. This is exemplified in example 1 and other examples. Claim 8's thionyl chloride appears at column 18, line 38, and claim 9's lutidine appears at line 40. Claim 34 is thus obvious, as such compounds are made in Example 1, step c and d; ex 3, steps d and e, example 6, steps b and c, etc. This compound has a different protecting group present, but that is obvious for reasons set forth above in the discussion of the R3 equivalences at column 3, lines 16-18, of methoxybenzyl with nitrobenzyl and allyl.

The claim 10-12 process is set forth at column 13, lines 27-50, including the use of acetone as solvent.. See examples 6, step b. The thiol intermediate at column 25, lines 29-31 renders claim 35 obvious. This compound has a different protecting group present, but that is obvious for reasons set forth above in the discussion of the R3 equivalences at column 3,

lines 16-18, of methoxybenzyl with nitrobenzyl and allyl. The compound is also made in examples 14-15, step b, although it is not named there, and is made in example 27, step e.

The traverse is unpersuasive. The remarks rely entirely on the declaration, but this is not persuasive. The declaration does not provide for a proper side-by-side comparison.

The sole difference between the two processes is the fact that the prior art uses p-methoxybenzyl as the protecting group, and applicants use p-nitrobenzyl. Applicants have not asserted any other difference. To demonstrate that this use of a different protecting group produces an unexpected effect, applicants must provided a side by side comparison. This has not been done.

Just as one example, in the PCl_5 reaction in the prior art, the base used was N-methyl morpholine, and the reaction was quenched with methanol and then water. In the instant example 1, the base used was α-picoline, and the reaction was quenched with isopropanol. Perhaps the difference between the two results was that applicants used a better choice of base or a better quenching agent. However, no claims are limited to the use of α-picoline, or to isopropanol in step (d). Applicants used a temperature range of –30° to –40°, whereas the prior art used -10±5° and subsequently allowed to rise to room temperature; perhaps the difference arose from that temperature difference. Again, no claim presents such a limitation. Hence, one cannot attribute the differences between the two to the different protecting group, since it is entirely possible that had applicants make the infelicitous choice of N-methyl morpholine and/or methanol and/or higher temperature, they might have had the same result.

A process comparison must reflect only the actual difference between the prior art process and the process of the claims. If there is an "welter of unfixed variables", the

comparison will not be persuasive, *In re Dunn* USPQ 479, 483. Such is clearly the case here.

There are other problems with the declaration as well. The actual experiments were not described in any specificity. Applicants simply gave the results ("an unacceptable high level of impurities"). This is particularly important in a case like this one where it appears that applicants got considerably poorer results than the prior art workers did.

In the other matter, applicants had next argued that their protecting group can be removed with sodium dithionate, and under "mild pH adjustment" whereas the prior art protecting group cannot. However, removing protecting groups is a well understood area, a routine matter, and these are all expected differences, not unexpected ones. Expected differences are not evidence of unobviousness, In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967); Ex parte Blanc, 13 USPQ2d 1383; In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Incidentally, applicants earlier statement that utilization of paramethoxybenzyl requires the use of Palladium is untrue. Hydrogenation is a common method, but such groups have been removed by other methods, such as formic acid, or TFA.

In the most recent remarks, applicants present the "second declaration". Again, this gives no actual examples, just a summary of results. Second, as noted above, the difference alleged has not been shown to be an unexpected difference. And most importantly, no present claim has this step. Patentability of a process cannot be based on a step which is not actually claimed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the

grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mark L. Berch
Primary Examiner
Art Unit 1624

9/16/05